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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

December 22, 2004

Ref: 2005-DAL-WL-7

WARNING LETTER

CERTIFIED MAIL
RETURNED RECEIPT REQUESTED

Mr. Robert (Skip) P. Cummins, President and CEO
Cyberonics, Inc.
100 Cyberonics Blvd.
Houston, Texas 77058 - 2017

Dear Mr. Cummins:

During an inspection of your firm's manufacturing operations located in Houston, Texas, on July 12 through September 15, 2004, United States Food and Drug Administration (FDA) Investigator, Ellen J. Tave, determined that your firm manufactures the Vagus Nerve Stimulator (VNS), an implanted generator that is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with medically intractable partial seizures. The VNS system includes a pulse generator, programming wand, programming software, electrode leads, tunneling tool, and accessory pack. This product is a device as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for their manufacturing, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) Regulation for medical devices, as specified in Title 21, Code of Federal Regulation (CFR), Part 820.

Quality System Regulation

At the close of the inspection, your firm was issued a list of inspectional observations, Form FDA-483 (copy enclosed), which identified a number of significant QS regulation violations including, but not limited to, the following:

1 Failure to completely investigate and evaluate the cause of each medical adverse event as required by 21 CFR 803.50(b)(2) and failure to maintain complete deliberation results as required by 21 CFR 803.18(b)(1)(i) [FDA-483, Item 1]. For example, your firm has not provided adequate documentation of deliberations to support your firm's decision making process for explaining why your firm could not reach a conclusion about the cause of (a) device migration reported in complaint file # 200306-0477 (reference MDR report # 2003-00402); and (b) high lead impedance, device migration, increase in seizures, and subsequent patient death reported in complaint file # 200312-0567 (reference MDR report # 2004-00030).

2. Failure to establish and maintain adequate procedures for validating the device design to ensure that the device conforms to user needs and intended uses and include design testing under actual or simulated use conditions as required by 21 CFR 820.30(g) [FDA 483, Item 2]. Evidence of your firm's design validation with regard to Model 102 is inadequate. For example:

   a) Evidence of design validation lacked supporting documentation to demonstrate how your simulated testing of the generator and the lead connecting to a [redacted] load actually simulated use conditions. For example, in an [redacted] chamber [redacted] maintained at [redacted] evidence was not provided which demonstrated the equivalence to the actual implanted generator and electrode connecting to the vagus nerve which resides in a fluidal or wet condition in the chest cavity (actual implant environment); and

   b) There was a lack of supporting documentation explaining why real time testing is not needed to verify the actual device longevity and a lack of evidence confirming the accuracy of your theoretical device life expectancy across patient programming ranges at the end of service voltage (actual use condition).

   c) The design validation does not appear to address the impact of possible increase in lead impedance of the electrode and vagus nerve interface during the course of patient therapy on battery life. Therefore, the accuracy of your theoretical estimate of device longevity is called into question; and

   d) The theoretical calculation of battery hours of operation does not appear to include or discuss the effect of the total number of patient magnet wipes (activations) on actual device longevity at nominal conditions in clinical settings (actual use condition); and

e) The design validation does not discuss or reference testing results of the ERI (Elective Replacement Indicator) flag under the various fault diagnostics conditions listed in the Physician's Manual (Section High Lead Impedance on a Diagnostic Test at Follow-up Visit).

3. Failure to investigate the cause of nonconformities relating to product, processes, and the quality system as required by 21 CFR 820.100(a)(2) [FDA-483, Items 3, 9, and 10]. For example:

a) Complaints of suspected end of service (EOS) were not considered as a product complaint, and there were no attempts to collect patient's programming data to evaluate if the devices reached normal/expected EOS; and

b) Your firm has not documented the death data by age categories to support data analysis required in CAPA Investigation Report INV 01-0006, dated January 8, 2002 and February 19, 2003. Your firm then concluded that there was no relationship seen in seizure changes among the 81 patients but reported that the patients responses to the VNS therapy were unknown or there was no information for 28 of 81 patients. Your firm also had not collected programming history data to assess the relationship of the amount of stimulation therapy at the time of death; and

c) CAPA investigation to verify a physician's observations that the devices delivered less current therapy than what were programmed during the last 6 to 12 months of device life had incomplete explanation of the results of Phase II and III testing; and

d) Product analysis (PA) of explanted generators did not show testing of the devices using the patients programming history to confirm or duplicate the patient complaints or non-complaints. For example, PA #5243, 4935, and 5600; and

e) Incident # 200310-1077 reported that a pediatric patient was implanted on December 18, 2002 and explanted on October 8, 2003 due to suspected end of service (EOS). The generator was implanted for almost 10 months. Your firm has not explained why the implanted generator did not set the ERI flag as it was approaching EOS. The user reported that the ERI flag did not set in spite of a high lead impedance reading. Your firm did not conduct duplicate testing of the explanted generator using the user's actual programming parameters to confirm the user's complaint of EOS. Your firm's product analysis documented that the explanted generator met its electrical specifications but did not explain (a) how your firm's electrical

testing results are related to the user's complaint, and (b) your firm's evaluation of the user report of normal diagnostics test results of high lead impedance in your product analysis report.

4. Failure to analyze processes, work operations, and other sources of quality data to identify existing and potential causes of non-conforming product as required by 21 CFR 820.100(a)(1) [FDA-483, Item 4, 6, and 11]. For example:

   a) Your firm has not documented, analyzed, and evaluated the reasons for both implants/reimplants and product returns to identify existing and potential causes of non-conforming product. Your firm does not know or explain how many reimplants were due to broken leads, suspected end of service (EOS), actual EOS, and high lead impedance; and

   b) User reports (non-complaints) of suspected EOS and confirmed EOS, and collected data on adverse events of asystole and bradycardia were omitted from [redacted] CAPA meetings; and

   c) Your firm has not analyzed complaints of high lead impedance, lead discontinuity, confirmed EOS, and suspected EOS to identify how many complaints were confirmed with an ERI (Elective Replacement Indicator) flag being set; and

   d) Your firm has not described the possible meaning of complaint conclusion code 40 in order to explain how complaints or adverse events were resolved with this conclusion code. It was found that conclusion code 40 was often used when the adverse events were resolved by device explants and reimplants. Review of complaint data queried by conclusion code 40 showed that your firm had classified 1081 complaints and 524 MDR reports using this code; and

   e) Your firm has neither collected nor analyzed patient programming history since 1997 in order to provide a theoretical estimate of actual device longevity over the entire implant population.

5. Failure to implement and record changes in methods and procedures needed to prevent and correct identified quality problems as required by 21 CFR 820.100(a)(5) [FDA-483, Item 6]. For example, although your firm has listed several potential causes of high lead impedance, your firm has not implemented the necessary solutions and verified their effectiveness in order to address numerous complaints of high lead impedance. A complaint log entitled "Lead Discontinuity, Suspected Lead Discontinuity, or High Lead

Impedance Incoming Complaints with Conclusions" for the period of January 1, 2002 through May 31, 2004 documented that 89 complaints were identified as a "design" issue.

6. Failure to establish and maintain procedures for implementing corrective and preventive action as required by 21 CFR 820.100(a) [FDA-483 Items 7 and 11]. For example, your firm (a) has not documented, analyzed, and evaluated the reasons for thousands of reimplants since 1997; (b) has not analyzed patient programming history data over the entire implant population; and (c) does not know how many reimplants were due to broken leads, suspected EOS, confirmed EOS, and high lead impedance, in order to validate input data used to calculate your firm's cumulative survival probability for the implanted generators. In addition, your firm has not explained how your device's survival probability curve matches the actual device longevity in clinical settings.

7. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit as required by 21 CFR 820.198(a). For example, your firm has not defined how your firm differentiates user complaints of suspected EOS from complaints of confirmed EOS, or high lead impedance.

Cyberonics' Response

We acknowledge receiving your letters with attachments, dated September 17, October 7, and December 8, 2004, responding to the Form FDA-483, Inspectional Observations, issued to your firm at the conclusion of our inspection on September 15, 2004. We have completed our review and determined that your response is incomplete. Your December 8th response was incomplete and did not provide any supporting information or evidence relating to the longevity verification. Your responses have not satisfactorily addressed the underlying issues. For example:

1 Your response did not clearly explain whether or not your firm considers user reports of suspected end of service (EOS) as a product complaint to be treated in accordance with 21 CFR 820.198(a). Your firm has not been able to determine the causes associated with many user reports of suspected EOS or high lead impedance or that your firm has not determined and documented how many reimplants were due to normal/actual EOS, suspected EOS, or high lead impedance. See your firm's investigation reports INV 02-0014, 02-0024, and 03-0016. Your firm also has not (a) explained whether your firm will attempt to collect patient programming history to aid your firm's investigation of complaints of suspected EOS or high lead impedance; and (b)

established procedures to indicate how your firm differentiates user complaints of suspected EOS from user complaints of actual EOS or high lead impedance to determine if in fact the devices were approaching or at their normal end of service based on the actual patient programming parameters. Your firm's investigation report 02-0014 was initiated in October, 2002 which recommended corrective actions to address user reports of high lead impedance. However, the completion dates for the proposed corrective actions were still classified "TBD" (To be Determined) at the time of the inspection.

2 Your firm has not been able to determine or explain how many reimplant cases were due to high lead impedance or other potential quality problems. Although you firm has identified several theoretical causes of high lead impedance complaints (user training, lead manufacturing defects, and design robustness), your firm has not completed the following proposed corrective actions. The effectiveness of these proposed corrective actions cannot be determined until you provide the results of your firm's monitoring of the high lead impedance complaints.

(a) Corrective Action Plan CAR 03-0003 addressing user training a potential cause of high lead impedance are in process without establishing an expected completion date; and

(b) Your response reported that Corrective Action Plan CAR 03-0004 addresses the handling of the Model 300 and Model 302 leads during manufacturing as a potential cause of high lead impedance was completed on July 16, 2004 during our inspection. You indicated manufacturing defects related to coil damage was not a significant cause of high lead impedance events. However, you have not explained what types of lead defects you found, specific steps your firm has taken or will take (a) to reduce incidents of lead manufacturing defects; (b) establish complaint investigation methods to differentiate user complaints of high lead impedance caused by a lack of user training from user complaints of high lead impedance caused by manufacturing lead defects; and

(c) [redacted] design project (DHF 0044) was initiated in [redacted] and is not expected to be completed until [redacted]

3. Your response implied that FDA's approval of your original PMA or subsequent PMA supplements means that FDA approves your firm's design controls. This is not true. Your firm's design control steps must be continuously maintained throughout the device design life cycle to ensure compliance with 21 CFR 820.30. Your response further stated that the

investigator attempted to inspect the safety and effectiveness of your devices. We disagree. The investigator explained that she did not inspect the safety and effectiveness of your devices epilepsy indication but rather she questioned the adequacy of your firm's design validation process concerning simulated testing of actual device implant conditions and device longevity.

4. Regarding simulated testing of actual implant environment, as part of your device failure investigation process, some of the explanted generators were actually tested in a [redacted] solution in order to investigate the complaint issues of suspected end of service, high lead impedance, or generators not delivering enough therapeutic currents as programmed. See your investigation reports INV 03-0016 and 02-0024. These two investigation reports documented that the explanted devices were placed in a [redacted] solution to simulate the actual implant environment. Your firm failed to explain how this type of testing is appropriately related to the original design validation testing of Model 100 in 1997, 101, and 102 in 2002.

5. Regarding real time testing to confirm device longevity, your response explained that performing the real time testing is inappropriate because it would require [redacted] to complete, and your mathematical equation for device longevity was based on "proven laws of math." First, your response has not explained why it takes [redacted] to conduct real time testing across all programming parameters. Second, you have not explained if your firm has (a) trended and/or documented the actual implant times of the clinical patients enrolled in the prior E01 – E05 studies using Model 100, the patients enrolled in the current Depression clinical study, or current non-clinical patients implanted with model 101 and 102, in order to compare their projected (theoretical) implant times to their actual implant times. Third, in your firm's Table 20 [Nominal Longevity Estimates Begin of Life (BOL) to End of Service (EOS)] listed in the electrical characterization report, your firm's longevity equation calculated that the device longevity would last [redacted] at a heavy stimulation setting of [redacted] and [redacted]% duty cycle. Real time testing at this rapid simulation setting would take about [redacted] not [redacted] to verify the accuracy of your theoretical device longevity equation.

6. Magnet Activations by Patients, you responded that the occurrence of manual magnet activations by patients would not cause any significant reduction of device longevity when compared to normal device stimulation. However, you acknowledged that your firm's extrapolation of energy consumption and rationales were not explained and documented in the design validation documents, e.g., electrical characterization report.

7. Your firm's current complaint handling procedure requires that a reply letter be sent to the complainant (physician) if your firm's complaint investigation resulted in "user error", and the user has not been notified of the error. The use of the VNS device for pediatric patients younger than 12 years of age is an unapproved use (off-label use), and therefore, adverse events related to this use are considered user error. See 21 CFR 803.3(d). In this situation, your firm did not follow its complaint handling procedures in that your firm had not sent reply letters to the complainants to notify them of user error concerning medical adverse events occurring in pediatric patients younger than 12 years of age. Our inspection documented that your firm had received 197 serious injury reports, 53 death reports, and 99 malfunction reports that were coded 212 (unapproved use of device) from January 1, 2002 through May, 14, 2004. Many of these medical adverse events were associated with the users using the VNS devices in pediatric patients younger than 12 years of age. We believe your firm should send a reply to each complainant in order to prevent further misuse, injury or other adverse situations from recurring. When the problem was caused by misuse, it is very important to advise the user to help prevent further misuse. If your firm believes there may be cases where a reply is not necessary, the record should state that no reply was made and the reason for not replying. Finally, although not sending a reply letter to the complainant is not a deviation of 21 CFR 820.198(e)(8), when a reply *is* sent it must be kept as part of the complaint file.

In summary of our review, your firm should implement a comprehensive QS action plan and provide FDA with status update reports outlining specific steps addressing the specific FDA-483 observations and issues identified in this letter and a global approach to correct and prevent any potential systemic problems.

Responding to This Letter

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and the regulations. The specific violations noted in this letter and in the Form FDA-483 issued at the close of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter of the specific steps you have taken, or will take to identify and correct the noted violations, including (1) the time frames within which the corrections will be completed, (2) any documentation indicating the corrections have been achieved, and (3) an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to ensure that similar violations will not recur. It is recommended that after responding to this letter that you have a meeting concurrently with both Dallas District Office and the Center for Devices and Radiological Health in order to facilitate appropriate technical discussion surrounding this letter and the inspection.

Your reply should be directed to Thao Ta, Compliance Officer, at the address indicated on the above letterhead.

Sincerely,

Michael A. Chappell
Dallas District Director

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